CIRRO The Lundbeck Foundation Center for Interventional Research in Radiation Oncology

Annual Report
June 2010

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Executive summary

Radiotherapy is one of the most dominating means of cancer treatment and plays an increasingly important role in the loco-regional management of many cancer types. The aim of the Lundbeck Foundation Center for Interventional Research in Radiation Oncology (CIRRO) is to establish individualized radiotherapy, which will lead to better tumour control with fewer side effects for a large proportion of cancer patients. This project encompasses biological, clinical and technical studies, which will form the basis for clinical implementation of biology-guided adaptive radiotherapy.

A structure for interaction between the involved institutions, activities, and implementations has been developed. In collaboration with all involved departments we have established work packages (WP) for translational research, and intervention protocols (IP) by which the clinical implementation of the various new methods in radiotherapy are being evaluated in phase I, II, and III protocols.

After a successful application in 2008, the centre started officially February 1, 2009 with a kick-off meeting for the 35 Danish experts and scientists involved in WPs and IPs. An academic coordinator was appointed March 2009, and the website www.cirro.dk was launched in April 2009. The scientific group had their first annual meeting in November 2009 with more than 60 scientists discussing ongoing and planned projects at a two-day meeting in Aarhus (see photo on front page).

The current report concerns the ongoing activities and results obtained after the first 18 months of operation.

CIRRO has a total budget of 90 mio. DKK (12 mio EUR). External funding has been obtained from a number of public and private sources, of which the 30 mio. DKK grant from the Lundbeck Foundation is by far the largest. Most of the budget for the Lundbeck Foundation grant has been allocated for PhD grants, fellowships and postdoc positions.

The CIRRO framework incorporates a total of 51 PhD projects (appendix 2), of which 5 are successfully completed by June 2010 (appendix 3). A total of 26 PhD projects are directly co-financed by grants from the Lundbeck Foundation. In addition, more than 40 senior scientists (post docs, fellows, consultants, associated professors, professors) are linked to the activities. For a complete list of the involved people, please see appendices 2 and 4 or www.cirro.dk.

CIRRO is currently involved in a total of 21 clinical intervention protocols (see pages 9-11), with a total of 481 patients so far included.

By June 2010, a total of 69 scientific papers have been published or accepted in peer reviewed international journals (appendix 1). Five PhD theses have been successfully defended. CIRRO has been involved in the organization of three international meetings and a PhD course in radiotherapy.

We believe that the ongoing and planned research in CIRRO is progressing as expected at an international, highly competitive level, and we are confident that the centre will meet the high expectations and aims.

June 2010

Jens Overgaard
Director

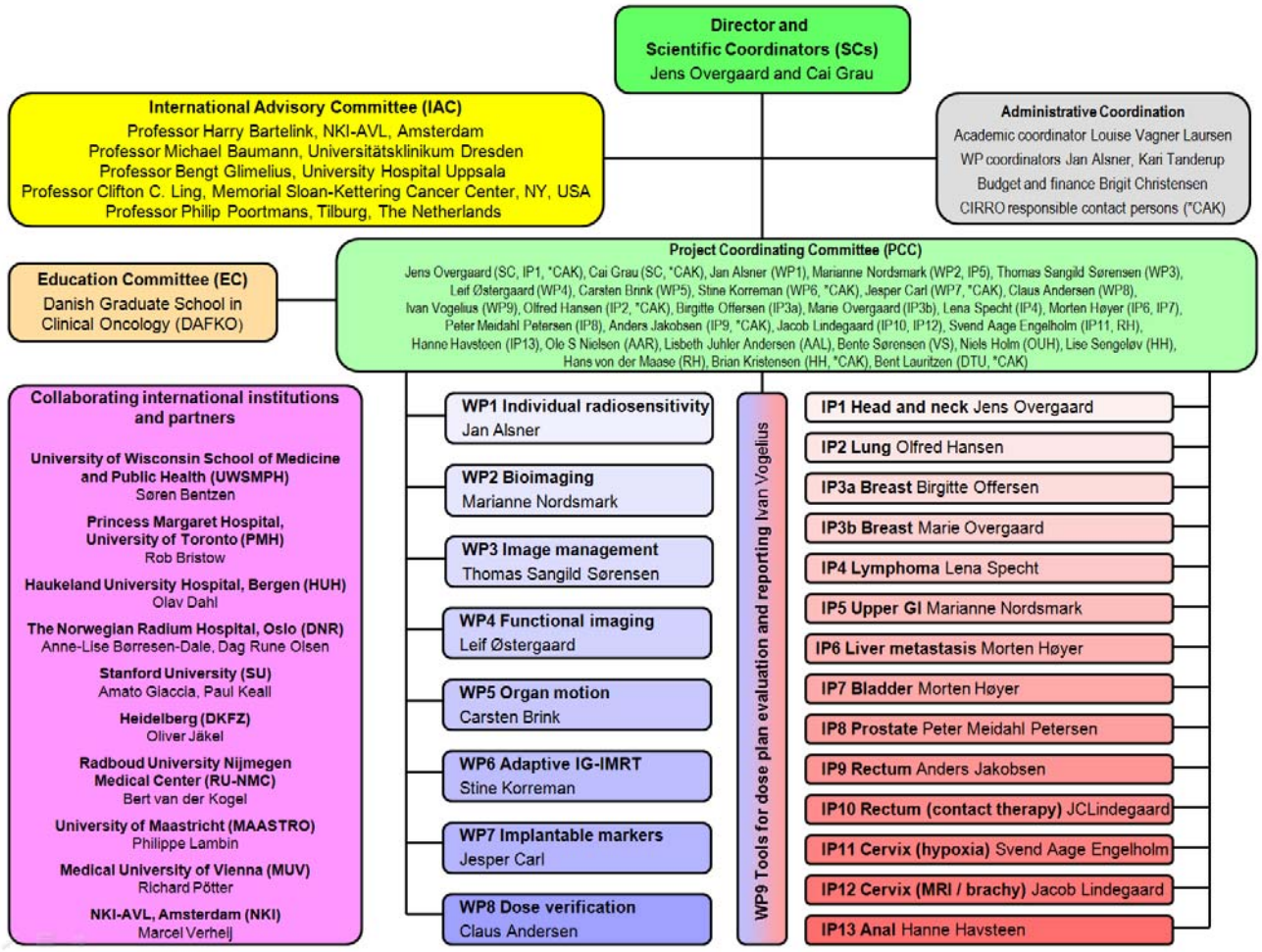
Cai Grau
Scientific Coordinator

Background and aim

Radiotherapy is one of the most dominating means of cancer treatment and plays an increasingly important role in the loco-regional management of many cancer types. The aim of the Lundbeck Foundation Center for Interventional Research in Radiation Oncology (CIRRO) is to establish individualized radiotherapy, which will lead to better tumour control with fewer side effects for a large proportion of cancer patients. This project encompasses biological, clinical and technical studies, which will form the basis for clinical implementation of biology-guided adaptive radiotherapy.

Structure and organisation

The organizational structure presented in the original application has been implemented, with the formation of WPs, IPs, and a Project Coordinating Committee (PCC). An academic coordinator was appointed March 2009. The administrative coordination has been strengthened by including CIRRO responsible contact persons from the participating centers. This reflected the need for smooth connection to the centers on a daily basis, which was not possible with the much larger PCC. The PCC has met so far twice, and the next meeting is planned in November 2010. The International Advisory Board has their first meeting in August 2010.



Workpackages

The status of the pre-clinical and translational research conducted in the nine WPs is outlined in the sections below. *In brackets are given references to the deliverables (D) and milestones (M) mentioned in the original application. Numbers of references refer to the reference list given i Appendix 1.*

WP01 - Individual radiosensitivity

The biology of tumour response to radiotherapy is studied using preclinical models and large high quality clinical material. Techniques to quantify DNA, RNA and protein level are applied in order to identify factors that can form the basis for individualized therapeutic intervention. Tumour microenvironment conditions affecting response to radiotherapy such as oxygen concentration, metabolism, and blood supply can be very heterogeneous between individual patients. Our preclinical studies have established a novel marker (gene expression signature) for identifying hypoxia independently of pH (D1.1). The hypoxia marker has been validated retrospectively, and by combining it with information on HPV status, it is possible to identify patients benefitting from a hypoxia-targeted therapy (D1.2, M1.2). Other markers for characterizing tumour microenvironmental conditions are currently being developed. Late morbidity like radiation-induced fibrosis greatly influences the quality of life of long term survivors of radiotherapy. Ability to predict the risk of morbidity is important to individualize radiotherapy treatment. The risk of radiation-induced morbidity varies between individuals and has a genetic component. A preclinical model for radiation-induced fibrosis has been developed (D1.3, M1.1). Furthermore a gene expression signature for predicting risk of radiation-induced fibrosis has been validated in an independent clinical dataset, and form part of the basis for ongoing genetic association studies (D1.3, M1.2). Genetic association studies are performed in collaboration with the newly established International Radiogenomics Consortium, where the WP leader is a member of the organizing committee.
WP leader: Jan Alsner, Aarhus. References: 3, 16, 17, 34, 35, 36, 37, 58, 59, 60, 68, 70, 71.

WP02 - Bioimaging – from experimental tool to clinical applicability

Tumour hypoxia is common and adversely affects loco-regional control and survival since hypoxic cells are radio-resistant. Tissue hypoxia can be studied non-invasively using PET tracers like ^{18}F-FAZA and ^{64}Cu-ATSM which are retained at low cellular pO_2, but the implications of some inherent limitations, like slow tracer kinetics, needs to be addressed. A number of studies using animal tumour models are ongoing or have been accomplished. Image contrast during hypoxia scans develop slowly which may compromise the hypoxia-specificity of simple static scan protocols. Accordingly, we have evaluated the possible advantage of pharmacokinetic analysis of dynamic data acquisition in PET scans (D2.1, M2.1) using tumour-bearing mice. The study shows that additional information may be derived from kinetic analysis of tissue time activity curves, but that classical compartmental models may be inappropriate in some tumour types. It remains unclear to what extent hypoxia-PET can identify treatment resistant tumours and tumours that will benefit from hypoxic intervention. Thus, we are currently assessing the ability of ^{18}F-FAZA-PET to predict the efficacy of radiotherapy in tumour-bearing mice either receiving or not receiving hypoxia-targeting intervention. The tumour microenvironment is highly dynamic and may change spontaneously or due to treatment, which in turn may compromise specialized treatment like IMRT. An ongoing study investigates the reproducibility of ^{18}F-FAZA-PET scans at baseline and during fractionated radiotherapy in tumour-bearing mice (D2.1, M2.1). Finally, a study on spontaneous canine tumours where the promising PET hypoxia marker ^{64}Cu-ATSM is compared to hypoxia-regulated genes and the immunologically-detectable hypoxia probe pimonidazole, progress as planned. Currently several dogs have been PET scanned and tumour-tissue sections have been analysed with autoradiography. The global and regional distribution of Cu-ATSM will next be compared to various genetic and morphological analyses of tissue sections and biopsies (D2.3). In addi-

tion, it is intended to do a head to head comparison between ^{64}Cu-ATSM and ^{18}F-FAZA PET in tumours. Four clinical protocols within CIRRO involve PET scanning with hypoxic tracers. Two protocols for head & neck cancer (CIRRO-IP010109 and CIRRO-IP010209) is using ^{18}F-FAZA. A protocol for cervix cancer (CIRRO-IP110110) involves both ^{18}F-FAZA and ^{64}Cu-ATSM PET. However, the use of ^{64}Cu-ATSM in human clinical trials is pending and the protocol is consequently not yet activated. One protocol in rectum cancer is in the planning phase.
WP leader: Marianne Nordsmark, Aarhus. References: 11, 12, 38, 52.

WP03 – Image management
The main objective of the studies is to develop reliable non-linear registration techniques to align all CT, MRI, and PET scans acquired during the course of treatment. The registrations can be used to develop the concept of adaptive radiotherapy treatment planning to account for changes in morphology and tumour biology encountered during a treatment course. Initially we have developed a technique to obtain non-linear registration of cone-beam CT to planning CT (M 3.1). It has already been evaluated in a few patients while the software is matured to support larger studies (expected 2011). Simultaneously, an additional iterative registration technique, guided by biomechanical physics, has been developed (D3.1). This is supplemented by ongoing work to estimate inter-fractional bladder motion using non-rigid registration of bladder surface meshes (D3.2). A valid registration of the bladder over multiple treatments makes it possible to compute the hot spot radiation more accurately. The goal is to allow higher doses in cases where the bladder incorrectly appears as a dose restricting organ due to overestimation of dose using crude addition of dose volume histograms (M3.3). Finally, an image sequence segmentation technique, which combines segmentation and registration in a joint framework, has been developed (supplement to M3.1).
WP leader: Thomas Sangild Sørensen, Aarhus. References: 41, 42, 61.

WP04 – Functional imaging
Studies focus on functional imaging used in preclinical and clinical settings to assess different characteristics of tumours and their microenvironment such as tumour volume, regional lymph node involvement, tumour biology, and response to radiotherapy. High resolution imaging of oxygen levels, hypoxia, metabolism and targeted nano-particles can be obtained by high-field MRI. Our work has so far led to the establishment of high-field ^{19}F MRI utilizing different ^{19}F labeled contrast agents (D4.1, M4.1). Preliminary experiments show signal from hexafluorobenzene (oximetry) in mouse tumours. High field implementation of DWI, DCE-MRI and susceptibility imaging with USPIO nano-particles has been established (D4.1, M4.1) and preliminary in vivo experiments in a mouse angiogenesis model show promising results. Clinical implementation and optimization of DWI sequence has been performed in patients (D4.2). Repetitive DWI MRI has been performed and analyzed in a cohort of patients (D4.4, M4.2) to characterize correlation between restricted diffusion regions and radiotherapy target volumes. A protocol for comparison of histopathology and functional imaging is to be submitted to the Ethical Committee by June 2010. Patient inclusion is expected from autumn 2010. Patients with operable cervical cancer will be subjected to functional imaging (MRI, PET-CT, DWI) prior to radical hysterectomy. The pathological specimen will be analyzed by conventional and hypoxia specific immunohistochemistry as well as autoradiography. MRI and PET-CT image information will be correlated with the histopathological findings. Another protocol is planned to compare and evaluate the sensitivity and specificity of FDG-PET, DWI, and MRI with administration of the nano-particle contrast agent USPIO to make lymph node assessment in patients with operable rectal and gyneacological cancer. However, availability of the contrast agent USPIO is pending for clinical use and this work is consequently delayed.
WP leader: Leif Østergaard, Aarhus. References: 10, 21, 22, 27, 40, 62, 63.

WP05 – Organ motion - 4D imaging and treatment

Knowledge of tumour position is vital to the exact delivery of the prescribed radiation dose. Tumours move during a treatment course due to e.g. weight loss but also within a single treatment session tumours can move due to e.g. breathing and bladder filling. Technologies exist to monitor tumour position during treatment (4D imaging) and delivery techniques which account for these movements are available at a research stage. The objectives are to further develop 4D treatment techniques and to implement these in clinical routine practice. Work has been performed on the uncertainty of the shape and volume of tumours outlined in 4D CT. Also the needed 4D CBCT quality for acceptable registration with 4D CT has been investigated (M5.1). Improvement of image quality by use of deformable registration is ongoing currently, by use of input from WP03 (M5.2). Tumour motion during treatment delivery is normally accounted for by adding margins to the treated volume such that the volume includes both the target and its anticipated motion. This approach is not optimal as it increases healthy tissue irradiation. An alternative approach for tumour motion management is dynamic multileaf collimator (DMLC) tracking which enables reduction of margins and thus reduced healthy tissue irradiation. Tracking is not yet used clinically with conventional linear accelerators. Recent research activities within CIRRO include the first demonstration of image-based tracking during intensity modulated arc therapy (IMAT), the first in vivo DMLC tracking of a mammal (using pigs, in collaboration with WP07, D7.3)), and integration of DMLC with an electromagnetic transponder that can be used for real-time prostate localization without the use of x-ray images.
WP leader: Carsten Brink, Odense. References: 18, 20, 39, 43, 53, 69, 74.

WP06 – Adaptive image-guided modulated radiotherapy

Both tumour and normal tissues undergo significant changes in size, shape, and position during a treatment course. A way to improve individualized radiotherapy is by adapting treatment plans with regard to the anatomical changes based on in-room imaging strategies. The “plan-of-the-day” scenario where replanning of treatment occurs on a daily basis is pursued. In-room imaging mainly refers to on-board cone-beam CT scanning which has a poorer soft tissue contrast than the planning fan beam CT scan. Therefore methods enabling use of CBCT scans to adapt treatment plans are needed. In one project delineation in CBCT has been successfully approached through propagation of structures from CT to CBCT scans (M6.1). Time-resolved diode dosimetry utility has been compared for dynamic arc radiotherapy for several commercial dosimetric systems (M6.1). Target and organs at risk (OAR) dose limits are studied by combining CT and CBCT scans for adaptive planning (M6.2). Studies on Monte Carlo simulations/full dose measurements by use of gel dosimetry are ongoing. Studies on optimization for optimal cost-effectiveness and integration with volumetric arc therapies are ongoing for various cancer sites (M6.3).
WP leader: Stine Korreman, Copenhagen. References: 9, 15, 30, 33, 47, 51, 56, 64, 65, 66, 73.

WP07 - Implantable markers for Image guided radiotherapy

The ability to deliver radiation dose accurately requires that the target is easily localized in the patient. Methods to facilitate tumour localization include the use of fiducial markers. Studies in this workpackage aim at developing and investigating three different fiducial markers: a Ni-Ti memory shape stent in prostate cancer and lung cancer (cone-beam CT), the X-ray contrast media lipiodol in bladder cancer (cone-beam CT), and a radiofrequent marker coil for definition of radioactive source catheters in brachytherapy (MRI).
The objective of several ongoing WP07 projects is to develop the use of Ni-Ti stent as a platform technology using the stent as X-ray fiducial image guided radiotherapy. The current status is that a clinical feasibility study using the Ni-Ti stent as a fiducial marker in prostate cancer radiotherapy has completed (M7.3). Clin-

ical protocols for retrospective and prospective follow-up studies have been developed, and is planned to start late 2010. A pre-clinical animal study of a prototype for a lung stent has been completed (M7.2). Results of this study were promising, but it also indicated that insertion and in particular removal of the stent demonstrated to be difficult and further development of the equipment was needed. Thus, a second pre-clinical animal study using technologically more advanced equipment is currently under way. Pending on the results from this study, a third pre-clinical study may be necessary. Protocols are underway for evaluation the accuracy and precision for the use of the fiducial marker in the lung, including reconstruction errors in respiration resolution scans (4D CT and 4D PET). Furthermore, design of a pre-clinical animal study to investigate risk factors of radiation pneumonitis using the stent technique is ongoing. A clinical trial for lung cancer patients is in preparation (M7.4). The projects will include virtual bronchoscope methods to estimate the expected optimal position of the stent relative to a given tumour in the lung and imaging and scoring methods for acute and late adverse effects from lung radiation. A CIRRO protocol (CIRRO-IP070109 - Image guided tumour boost of localized unifocal c. vesica urinaria) for using lipiodol as a fiducial marker in bladder cancer is currently active and data from the first patients have been analyzed. The results demonstrate so far that lipiodol can successfully be injected into the bladder mucosa and subsequently visualized on CT and CBCT as a fiducial marker (M7.1).
WP leader: Jesper Carl, Aalborg. References: 13, 24, 25, 57.

WP08 - Dose verification

Development and use of new dose verification procedures will improve safety and precision of individualized radiotherapy. Projects explore novel techniques based on dosimetry and Monte Carlo calculations. A new dose verification protocol using time resolved online *in vivo* dosimetry in brachytherapy of cervical cancer patients has been developed and evaluated in five patients. The work suggests that improved dose verification can be achieved using time-resolved luminescence dosimetry directly in the tumour region (D8.1). A larger study is now prepared, and the technique is being modified for high-dose rate brachytherapy of prostate cancer patients. Concerning Monte Carlo based treatment plans for advanced radiotherapy a complete workflow has been established at Herlev which allows for automatic Monte Carlo recalculation of treatment plans for dynamic radiotherapy such as IMRT and Rapid Arc. The main result is a study which further underlines the inaccuracies introduced when conventional treatment planning systems are used for dose calculations in geometries involving large density variations (D8.3). Studies on reference dosimetry are ongoing and a conjunction of experimental techniques and Monte Carlo computations has been carried out. The study suggests that alanine detectors with a volume of 2.5x2.5x2.5 mm^3 are indeed suitable for both reference output factor determination in solid water phantoms (at least for 6 MV beams) and small-field dosimetry in general.
WP leader: Claus Andersen, DTU. References: 1,2.

WP09 – Tools for dose plan evaluation and reporting

The main objective is to develop feasible and effective tools for reporting and analyzing radiotherapy planning, delivery, and outcome data. The ultimate aim is to develop a national database containing 3D/4D treatment data and outcome for all patients undergoing radiotherapy in Denmark. An analysis of existing tools for dose plans reporting resulted in the choice of a Conquest DICOM-RT database for dose plan archiving. User rights and access control is improved through a supplementary web-based interface, which have been designed for this purpose (D9.1). Secure communications is achieved through an external partner, MedCom. A tool for automatic reporting of radiotherapy dose plans has been designed. Odense University

Hospital and Vejle Hospital have fully verified communications, Rigshospitalet and Århus University Hospital have full connections but some functionality remains to be tested. Radiotherapy dose plans from the clinical protocols in breast cancer, CIRRO-IP030109 and CIRRO-IP030209, are at present being stored in the database.
WP leader: Ivan Vogelius, Copenhagen.

Intervention protocols

The aim of the clinical intervention protocols is to test the biological and technical developments in phase I, II and III clinical multicenter trials on a national scale.

By June 2010 a total of 21 protocols were active or planned. A total of 481 patients have been included in 15 protocols (two of which are closed), and 4 protocols are planned to start recruitment in 2010. The detailed status of the IPs is listed below:

- **CIRRO-IP010109 – Identification of tumour hypoxia by ^{18}F-FAZA PET scanning in patients with operable head and neck carcinoma** [Bestemmelse af tumor hypoksi med 18F-FAZA Positron Emissions Tomografi i tumorer hos patienter med operabel hoved-hals karcinom (DAHANCA 23)] PI: Lise Saksø Mortensen, AUH. Status: Activation expected fall 2010.
- **CIRRO-IP010209 – Prognostic value of ^{18}F-FAZA PET scans following primary radiotherapy in patients with head and neck carcinoma** [Den prognostiske værdi af 18F-FAZA Positron Emissions Tomografi hos patienter med hoved-hals karcinom efter primær strålebehandling (DAHANCA 24)] PI: Lise Saksø Mortensen, AUH. Status: Protocol active. 5 patients accrued. Participating departments: Aarhus, Odense.
- **CIRRO-IP010309 – Resistance training and dietary supplements as intervention for regaining muscle mass following radiotherapy in head and neck cancer patients** [Styrketræning kombineret med kosttilskud som intervention til genopbygning af muskelmasse efter strålebehandling for hoved-hals cancer (DAHANCA 25A)]
  PI: Simon Lønbro, AU. Status: Protocol active. 2 patients accrued. Participating departments: Aarhus, Odense, Herlev.
- **CIRRO-IP020109** - **NARLAL - Navelbine And Radiotherapy in Locally Advanced Lung cancer**
  PI: Olfred Hansen, OUH. Status: Protocol active. 6 patients accrued. Participating departments: Odense, Aarhus, Aalborg, Vejle, Herlev, Rigshospitalet.
- **CIRRO-IP020209** - **TARLAL - Tarceva And Radiotherapy in Locally Advanced Lung cancer**
  PI: Olfred Hansen, OUH. Status: Protocol active. 3 patients accrued. Participating departments: Odense, Aarhus, Vejle.
- **CIRRO-IP030109 – A randomized trial of Partial Breast Irradiation (PBI) in node-negative early breast cancer.**
  PI: Birgitte Offersen, AUH. Status: Protocol active. 71 patients accrued. Participating departments: Aarhus, Aalborg, Vejle, Odense, Rigshospitalet (Herlev expected to start up soon).
- **CIRRO-IP030209** - **Hypofractionated adjuvant radiotherapy in node-negative early breast cancer**
  PI: Marie Overgaard, AUH. Status: Protocol active. 170 patients accrued. Participating departments: Aarhus, Aalborg, Vejle, Odense.

- **CIRRO-IP040110** - **Reduction of risk of long-term complications of radiotherapy for lymphomas.**
  PI: Lena Specht, RH. Status: Protocol active. 3 patients accrued. Participating departments: Rigshospitalet
- **CIRRO-IP050109** - **CRITICS-study: ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach.**
  PI: Marianne Nordsmark, AUH. Status: Protocol awaiting approval from the local Ethical Committee. Activation expected fall 2010.
- **CIRRO-IP060109** - **RAS-trial: Radiofrequency ablation versus stereotactic body radiation therapy for colorectal liver metastases: A randomized trial.**
  PI: Morten Høyer, AUH. Status: Activation expected September 2010. Participating departments: Aarhus, Odense.
- **CIRRO-IP070109 – Image guided tumour boost of localized unifocal c. vesica urinaria** [Billedvejledt tumorboost af lokaliseret unifokal c. vesica urinaria: Et fase I/II project].
  PI: Jimmi Søndergaard, AUH. Status: Protocol active. 6 patients accrued. Participating departments: Aarhus, Herlev, Rigshospitalet, Odense.
- **CIRRO-IP080109 - Hypo-RT-PC: Study on hypofractionated radiotherapy in intermediary risk prostate cancer patients** [Fase III studie om hypofraktioneret stråleterapi til patienter med prostatacancer i intermediær risikogruppe].
  PI: Morten Høyer, AUH. Status: Protocol active. No patients accrued in Denmark yet (200 in Sweden). Participating departments: Aarhus, Odense, Herlev.
- **CIRRO-IP080209 - PROPEL A+B Pelvine lymph node irradiation with concomitant boost to the prostate in high risk prostate cancer patients** [Pelvin lymfeknudebestråling med samtidigt boost til prostata for prostatakræftpatienter i høj-risikogruppe: Et fase I/II studium].
  PI: Lise Bentzen, AUH. Status: Activation expected fall 2010. Participating departments: Aalborg, Aarhus, Odense, Vejle, Herlev and Rigshospitalet
- **CIRRO-IP080110 – A new everyday life – Rehabilitation and mastering late effects of radiotherapy for prostate cancer** [En ny hverdag - Rehabilitering og mestring af senfølger efter kurativ strålebehandling for prostatacancer].
  PI: Karin Dieperink, OUH. Status: Protocol active. 51 patients accrued. Participating departments: Odense
- **CIRRO-IP090109 - Watchful Waiting in rectal cancer: A prospective observational study of rectal cancer patients after concomitant chemoradiotherapy** [Watchful waiting: Et prospektivt observationsstudie af patienter med cancer recti efter concomitant strålebehandling og kemoterapi].
  PI: Anders Jakobsen, Vejle. Status: Protocol active. 5 patients accrued. Participating departments: Vejle (treating patients from other departments also)
- **CIRRO-IP090209 – Contrast enhanced transrectal ultrasound scanning of rectal cancer patients** [Kontrast forstærket transrektal ultralydskanning af patienter med rektal cancer].
  PI: Anders Jakobsen, Vejle. Status: Protocol active. 2 patients accrued. Participating departments: Vejle (treating patients from other departments also)

- **CIRRO-IP090309 – Consecutive rectoscopies in connection with pre-operative chemo-radiotherapy of rectal tumours** [Konsekutive rektoskopier foretaget i forbindelse med præ-operativ kemostråleterapi af rektum tumorer på Vejle Sygehus].
  PI: Anders Jakobsen, Vejle. Status: Protocol closed. 100 patients accrued. Participating departments: Vejle (treating patients from other departments also)
- **CIRRO-IP100110 – Observational study on contact X-ray and transanal endoscopic microsurgery in curative treatment of rectal cancer (CONTEM).**
  PI: Jacob Lindegaard, AUH. Status: Protocol awaiting delivery of equipment.
- **CIRRO-IP110110 – Feasibility study for the purpose of introducing hyoxia tracers in patients with cervical cancer** [Feasibility studium med henblik på introduktion af hypoksi tracer hos patienter med cervixcancer].
  PI: Svend Aage Engelholm, RH. Status: Protocol not yet initiated. Clinical use of Cu-ATSM PET tracer is pending.
- **CIRRO-IP120109 - EMBRACE: An International Study on MRI-guided Brachytherapy in Locally Advanced Cervical Cancer.**
  PI: Jacob Lindegaard, AUH. Status: Protocol active. 34 patients accrued in Aarhus (223 in total). Participating departments: Aarhus.
- **CIRRO-IP130109 – IMANAL: PET-CT scans and MRI in anal cancer patients** [PET-CT skanning og MR ved analcancer].
  PI: Hanne Havsteen, Herlev. Status: Protocol closed. 22 patients accrued. Participating departments: Herlev

PhD projects

A total of 46 ongoing PhD projects are linked to the activities (WP or IP) in CIRRO, and a major part of the grant from the Lundbeck Foundation is used to actively co-financing 21 of these PhD projects.

Five PhD's and one Master's student associated with CIRRO have successfully defended their projects and theses.

CIRRO PhD students are all affiliated with DAFKO (Danish Graduate School in Clinical Oncology). Together with DAFKO, CIRRO organized a one week PhD course in radiotherapy in November 2009.

Meetings and seminars

In addition to funding scientific projects CIRRO has organised, sponsored or supported a number of activities.

A **kick-off meeting** was organized at Koldkærgård Conference Center in Aarhus February 17-18 2009 with 35 participants. The focus was to present and discuss the planned activities of the centre.

In November 23-24, 2009, the **1st annual CIRRO meeting** was held, also at Koldkærgård Conference Center in Aarhus. A total of 66 participants were present to discuss the ongoing activities in the center.

In conjunction with the annual meeting, a three-day **PhD course** on biology, imaging and technology in radiation oncology was organized at Aarhus University in collaboration with the Danish Graduate School in Clinical Oncology. A total of 28 PhD students attended the course.

The international Tumour Microenvironment Workshop in Toronto, May 2-5 2010 was sponsored and co-organized by CIRRO, which was also represented with nine oral presentations. Other co-organizers included two research centers similar to CIRRO, namely the German "Center for Radiation Research in Oncology (OncoRay)" and the Canadian center "Spatio-Temporal Targeting and Amplification of Radiation Response (STTARR)".

CIRRO was co-organizer of the **Acta Oncologica symposium BiGART2010** (Biology Guided Adaptive Radiotherapy) in Aarhus, May 26-28 2010. This international meeting had a strong international faculty and attracted more than 140 participants, of which 58 were from CIRRO. The proceedings of the meeting are published as a special issue of Acta Oncologica.

CIRRO co-organized the **4th Danish workshop for Proton and Heavy-Ion Dosimetry** in Aahus, November 16-18, 2009.

Other activities included seminars in radiation injuries in pelvis minor (April 8 2010), WP09 user meeting (April 19, 2010) and meetings with CIRRO responsible contact persons (CAK) from the participating departments (four per year).

Upcoming events include meeting with the International Advisory Committee at Schæffergården, August 26-27 2010, a PhD course at Koldkærgård in November 2010 and the 2nd annual CIRRO meeting at Koldkærgård, November 25-26 2010.

Homepage

CIRRO launched the homepage www.cirro.dk in April 2009. The website is our preferred platform of information both for members of CIRRO and the public. The website gives an overview of the research activities within the center as well as listing news, publications, events etc. All CIRRO members are expected to register and create a public profile at the homepage.

Economy

The total 5-year budget for CIRRO is 90 mio. DKK. The Lundbeck Foundation is the main contributor with 30 mio. DKK. The remaining 60 mio. DKK has been obtained from institutional support to permanent staff, establishment of new research positions and external grants from a large number of private and public sources. Among major co-sponsors are:

- The Danish Council for Strategic Research (Programme on Health, Food, and Welfare)
- Danish Council for Independent Research
- Aarhus University
- Aarhus University Hospital
- The Danish Cancer Society
- Varian Medical Systems
- Elekta

The grant from the Lundbeck Foundation is allocated mainly to salary for scientific personnel. A minor part is used for supporting travel and meetings. The funds are allocated to projects initiated in 2009 or starting during 2010, since the aim is to have all funded projects completed and published before the end of the project in 2014.

For 2009, total expenses covered by the grant from the Lundbeck Foundation were 5.101.000 DKK, which was in good agreement with the planned budget (5.154.000 DKK). The submitted budgets for 2010 and 2011 remain unchanged.

Concluding remarks

We believe that the ongoing and planned research in CIRRO is progressing as expected at an international, highly competitive level, and we are confident that the centre will meet the high expectations and aims.

Appendix 1: List of scientific publications, per June 2010

1. Andersen CE, Nielsen SK, Greilich S, Helt-Hansen J, Lindegaard JC, Tanderup K. Characterization of a fiber-coupled Al2O3:C luminescence dosimetry system for online in vivo dose verification during 192Ir brachytherapy. Med Phys. 36: 708-18, 2009.
2. Andersen CE, Nielsen SK, Lindegaard JC, Tanderup K. Time-resolved in vivo luminescence dosimetry for online error detection in pulsed dose-rate brachytherapy. Med Phys. 36: 5033-43, 2009.
3. Andreassen CN, Alsner J. Genetic variants and normal tissue toxicity after radiotherapy: A systematic review. Radiother Oncol. 92: 299-309, 2009.
4. Bassler N, Holzscheiter M. Calculated LET Spectrum from Antiproton Beams Stopping in Water. Acta Oncol. 48: 223-226, 2009.
5. Bassler N, Holzscheiter MH, Petersen JB. Neutron Fluence in Antiproton Radiotherapy, Measurements and Simulations. Acta Oncol. (in press).
6. Bassler N, Jäkel O, Søndergaard CS, Petersen JB. Dose-and LET-painting with particle therapy. Acta Oncol. (in press).
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42. Noe, KØ. Deformable Image Registration for Use in Radiotherapy. PhD Thesis, Faculty of Science, University of Aarhus, 2009.
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65. Thörnqvist S, Petersen JB, Høyer M, Bentzen LN, Muren LP. Propagation of target and organ at risk contours in radiotherapy of prostate cancer using deformable image registration. Acta Oncol. (in press).
66. Vestergaard A, Søndergaard J, Petersen JB, Høyer M, Muren LP. A comparison of three different adaptive strategies in image-guided radiotherapy of bladder cancer. Acta Oncol. (in press).
67. Vogelius IS, Westerly DC, Cannon GM, Bentzen SM. Hypofractionation does not increase radiation pneumonitis risk with modern conformal radiation delivery techniques. Acta Oncol. (in press).
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71. Wojdacz, Tomasz. Methylation Sensitive High Resolution Melting (MS-HRM) - development and application in cancer research and diagnostics. PhD Thesis, Faculty of Health Sciences, University of Aarhus, 2010.
72. Worm ES, Hansen AT, Petersen JB, Muren LP, Præstegaard LH, Høyer M. Inter- and intra-fractional localisation errors in cone-beam CT guided stereotactic radiation therapy of tumors in the liver and lung. Acta Oncol. (in press).
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Appendix 2: CIRRO affiliated PhD projects and students

1. Andreassen, Camilla Mondrup: Volume effects in NTCP models. Aarhus University (enrolled 2009).
2. Appelt, Ane: Evaluation of dose plan quality with focus on prediction of side-effects following radiotherapy of lung and rectum [Evaluering af dosisplankvalitet med fokus på prædiktion af bivirkninger ved strålebehandling af lunge og rectum]. University of Southern Denmark (enrolled 2010).
3. Bertelsen, Anders: Volumetric Modulated Arc Therapy (VMAT®) - advantages and disadvantages. University of Southern Denmark (enrolled 2008)
4. Bjerre, Troels: Automated image-based procedures for radio-therapy treatment evaluation and daily dose re-planning. Danish Technical University (enrolled 2010)
5. Bøje, Charlotte: The importance of comorbidity for the outcome of radiotherapy for head and neck cancer. Aarhus University (enrolled 2009)
6. Christoffersen, Christian: Motion compensated image reconstruction. Aarhus University (enrolled 2010)
7. D'Andrea, Filippo: Genetic or microenvironmental origin of radioresistance in sarcoma) Studies in mesenchymal cancer stem cells derived soft tissue sarcoma model. Aarhus University (enrolled 2007)
8. Dieperink, Karin: A new everyday life – rehabilitation and mastering late effects of radiotherapy for prostate cancer [En ny hverdag - Rehabilitering og mestring af senfølger efter kurativ strålebehandling for prostatacancer]. University of Southern Denmark (enrolled 2009)
9. Due, Anne Kirkebjerg: Imaging and tumour definition in IMRT of head and neck cancer [Billeddannelse og tumordefinition ved IMRT af hoved-halscancer]. Copenhagen University (enrolled 2009)
10. Elstrøm, Ulrik Vindelev: Image-guided adaptive radiotherapy of head and neck cancer. Aarhus University (enrolled 2007)
11. Emmertsen, Katrine: Influence of neoadjuvant radiotherapy on bowel, urinary and sexual function after treatment for rectal cancer. Aarhus University (enrolled 2008)
12. Gottlieb, Karina Lindberg: Investigation of respiration induced intra- and inter-fractional tumour motion using a standard Cone Beam CT. University of Southern Denmark (enrolled 2009)
13. Grantzau, Trine: Risk of second primary cancer among Danish women with breast cancer treated with postoperative radiotherapy. Aarhus University (enrolled 2010).
14. Haack, Søren: Diffusion Weighted MRI for Radiotherapy Planning. Aarhus University (enrolled 2009)
15. Hansen, Anders Elias: Characterization, regulation and the role ofhypoxia and markers of hypoxia to radiotherapy of canine soft tissue sarcomas *a spontaneous model of human disease. Copenhagen University (enrolled 2009)
16. Havelund, Birgitte Mayland: Clinical aspects of hypoxia-inducible factors in colorectal cancer [Kliniske aspekter af hypoksi-inducible faktorer ved colorectal cancer]. University of Southern Denmark (enrolled 2009)
17. Herrmann, Rochus: Investigation of dosimetric and radiobiological models for particle therapy. Aarhus University (enrolled 2009)
18. Hoff, Camilla: Importance of Hemoglobin Concentration and its Modification for the Outcome of Head and Neck Cancer Patients treated with Radiotherapy. Aarhus University (enrolled 2007)

19. Josephsen, Norah: Radiation-induced hypothyroidism in head-and-neck cancer. University of Southern Denmark (enrolled 2010)
20. Kaiser, Franz-Joachim: Novel Dosimetry Methods in Heavy Charged Particle Beams. Aarhus University (enrolled 2010)
21. Kallehauge, Jesper: Functional Imaging for Individualized Adaptive Radiotherapy in Locally Advanced Cervical Cancer. Aarhus University (enrolled 2010)
22. Kertzscher, Gustavo. Danish Technical University.
23. Lassen, P. The role of Human papillomavirus in head and neck cancer and the impact on radiothe-rapy outcome. Aarhus University, project completed 2010.
24. Lønbro, Simon: Resistance training and dietary supplements as intervention for regaining muscle mass following radiotherapy in head and neck cancer patients. Aarhus University (enrolled 2009)
25. Lyngholm, Christina: Breast Conserving Therapy (BCT) Cosmetic outcome and longterm adverse reactions in the DBCG 89-protocol. Aarhus University (enrolled 2009)
26. Møller, Søren: Clinical applications of O-(2-[18F]fluoroethyl)-L-tyrosine (FET) PET in patients with gliomas. Copenhagen University (enrolled 2010)
27. Mortensen, Hanne Rahbek: Reduction of dysphagia-related morbidity in head and neck radiotherapy. Aarhus University (enrolled 2010)
28. Mortensen, Lise Saksø: 4D biological imaging of hypoxia in human tumours. Aarhus University (enrolled 2008)
29. Nawroth, Isabel: Intervention studies for Radiation-induced fibrosis (RIF) using RNA interference. Aarhus University (enrolled 2008)
30. Nielsen, Martin Skovmos: Precision and accuracy in Image Guided RT. Impact of NiTi stent for lung cancer patients. Aalborg University (enrolled 2010)
31. Nielsen, Mette Bak: Role of extensive surgery with or without interstitial brachytherapy in advanced primary or locally recurrent rectal cancer. Aarhus University (enrolled 2009)
32. Nielsen, Tine Bjørn: Organ motion - 4D imaging and treatment. University of Southern Denmark (enrolled 2009)
33. Noe, KØ. Deformable Image Registration for Use in Radiotherapy. Aarhus University, project completed 2009.
34. Nygaard, Ditte Eklund: Modelling of positional tumour variations in 4D [Modellering af positionelle tumor-variationer i 4D] Copenhagen University (enrolled 2009)
35. Ottosson, Rickard: Monte Carlo based treatment plans for radiotherapy: Evaluation and optimization of modern treatment planning and treatment techniques. Danish Technical University (enrolled 2010)
36. Pagh, Anja: Optimization of brachytherapy in locally advanced cervical cancer by repetitive functional MRI. Aarhus University (enrolled 2010)
37. Petersen, Stine Elleberg: Morbidity in patients with prostate cancer treated with radiation therapy. Aarhus University (enrolled 2010)
38. Sander, Lotte: Side effects following use of a Ni Ti stent as a marker in radiotherapy of prostate cancer [Bivirkninger efter brug af Nikkel Titanium stent som markør ved intenderet kurativ strålebehandling for prostatacancer]. Aalborg University (enrolled 2010)
39. Schytte, Tine: Clinical advantages and disadvanteges of optimized radiation therapy and planning as a respiratory guided planning and rotation IMRT in conjunction with altered radiation dose and the addition of radiation potentiating drugs [Kliniske fordele og ulemper ved optimeret stråleplanlægning og terapi som respirations vejledt planlægning og rotations IMRT sammenholdt med ændret stråledosis og tillæg af stråleforstærkende medicin]. University of Southern Denmark (enrolled 2009)

40. Serup-Hansen, Eva: Tumourmarkers and the predictive value of MRI and PET-CT scans in concomitant chemoradiotherapy of anal cancer [Tumormarkører og den prædiktive værdi af serielle MR og PET-CT scanninger ved konkomitant kemostrålebehandling af analcancer]. Copenhagen University (enrolled 2010)
41. Skyt, Peter Sandegaard: Three-dimensional dosimetry in radiotherapy using new polymer materials and optical tomography. Aarhus University (enrolled 2009)
42. Søndergaard, Jimmi: Image guided tumour boost of localized unifocal c. vesica urinaria [Billedvejledt tumorboost af lokaliseret unifokal c. vesica urinaria: Et fase I/II project]. Aarhus University (enrolled 2008)
43. Sørensen, BS: Influence of tumour microenvironmental factors on endogenous markers of hypoxia. Aarhus University, project completed 2009.
44. Thor, Maria: Prediction of adverse effects in pelvic radiotherapy incorporating normal tissue position and biology patterns. Aarhus University (enrolled 2010)
45. Thörnqvist, Sara: Robust treatment planning to account for variations in target position and function for RT of locally advanced prostate cancer. Aarhus University (enrolled 2009)
46. Toustrup, Kasper: Tumour Microenvironment, Hypoxia and Gene Expression Signatures in Squamous Cell Carcinomas of the Head and Neck. Aarhus University (enrolled 2007)
47. Tramm, Trine: Gene expression analysis on RNA extracted from archival paraffin-embedded tissue from a cohort of breast cancers. Aarhus University (enrolled 2007)
48. Wiechec, E. Characterization of new breast cancer susceptibility genes with impact on prognosis and design of novel anticancer therapies. Aarhus University, project completed 2010.
49. Wojdacz, Tomasz. Methylation Sensitive High Resolution Melting (MS-HRM) - development and application in cancer research and diagnostics. Aarhus University, project completed 2010.
50. Worm, Esben: Liver tumour motion during radiotherapy. Aarhus University (enrolled 2010)
51. Wright, Pauliina: Development and modelling of image-guided adaptive radiotherapy strategies for bladder cancer. Aarhus University project completed 2010.

Appendix 3: Dissertations by CIRRO affiliated students

PhD degree

1. Noe, KØ. Deformable Image Registration for Use in Radiotherapy. PhD Thesis, Faculty of Science, University of Aarhus. Defended October 1 2009.
2. Sørensen, BS. Influence of tumour microenvironmental factors on endogenous markers of hypoxia. PhD Thesis, Faculty of Health Sciences, University of Aarhus. Defended November 6 2009.
3. Wiechec, E. Characterization of new breast cancer susceptibility genes with impact on prognosis and design of novel anticancer therapies. PhD Thesis, Faculty of Health Sciences, University of Aarhus. Defended May 28 2010.
4. Wojdacz, Tomasz. Methylation Sensitive High Resolution Melting (MS-HRM) - development and application in cancer research and diagnostics. PhD Thesis, Faculty of Health Sciences, University of Aarhus. Defended June 4 2010.
5. Lassen, P. The role of Human papillomavirus in head and neck cancer and the impact on radiotherapy outcome. PhD Thesis, Faculty of Health Sciences, University of Aarhus. Defended June 18 2010.

Masters degree

1. Kofoed, T. Image quality of 4DCT scans. Master's Thesis, Niels Bohr Institute, University of Copenhagen. May 2009.

Appendix 4: CIRRO affiliated senior scientists

1. Alsner, Jan. Associate professor, AUH. WP01 leader. WP coordinator.
2. Andersen Claus. Associate professor, Risø-DTU. WP08 leader.
3. Andreassen, Nicolaj. MD PhD, AUH.
4. Bangsgaard, Jens-Peter. Medical physicist, RH. CAK.
5. Bassler, Niels. Associate professor, AU.
6. Behrens, Claus. Physicist PhD, Herlev.
7. Bentzen, Lise. MD PhD, AUH.
8. Brink, Carsten. Associate professor, OUH. WP05 leader.
9. Busk, Morten. Senior scientist PhD, AUH
10. Carl, Jesper. Chief physicist, Aalborg. WP07 leader, CAK
11. Engelholm, Svend Aage. Professor MD, RH. IP11 coordinator.
12. Eriksen, Jesper Grau. MD PhD, OUH
13. Fledelius, Walther. Postdoc, AUH
14. Grau, Cai. Professor MD, AUH. Scientific coordinator. CAK
15. Hansen, Olfred. MD PhD, OUH. IP02 coordinator. CAK
16. Havsteen, Hanne. MD PhD, Herlev. IP13 coordinator
17. Helt-Hansen, Jakob. Senior scientist, Risø-DTU
18. Høyer, Morten. Associate professor MD, AUH. IP06 and IP08 coordinator.
19. Jakobsen, Anders. Professor MD, Vejle. IP09 coordinator. CAK
20. Johansen, Jørgen. MD PhD, OUH
21. Korreman, Stine. Director of Physics Research, RH. WP06 leader. CAK.
22. Kristensen, Brian. Chief physicist, Herlev. CAK
23. Larsen, Rasmus. Professor, DTU.
24. Laursen, Louise Vagner. Academic coordinator, post doc. AUH
25. Lauritzen, Bent. Head of programme, Risø-DTU. CAK
26. Lindegaard, Jacob. Associate professor MD, AUH. IP10 and IP 12 coordinator.
27. Lühr, Armin. Postdoc, AU.
28. Muren, Ludvig. Associate professor, AUH
29. Nielsen, Thomas. Postdoc, AUH
30. Nordsmark, Marianne. MD PhD, AUH. WP02 leader and IP05 coordinator.
31. Nørrevang, Ole. Chief physicist, AUH
32. Offersen, Birgitte. MD PhD, AUH. IP03 coordinator.
33. Overgaard, Jens. Professor MD, AUH. Director. IP01 coordinator
34. Overgaard, Marie. MD, AUH. IP03 coordinator.
35. Pedersen, Erik Morre. MD PhD, AUH
36. Petersen, Jørgen. Senior scientist PhD, AUH.
37. Petersen, Peter Meidahl. MD PhD, RH. IP08 leader.
38. Poulsen, Per Rugaard. Senior scientist PhD, AUH.
39. Skogholt, Peter. Medical physicist, Vejle Sygehus.
40. Sørensen, Brita Singers. Postdoc, AUH.
41. Sørensen, Thomas Sangild. Associate professor, AU. WP03 leader.
42. Specht, Lena. Professor MD, RH. IP04 coordinator.
43. Tanderup, Kari. Postdoc, AUH. WP coordinator.
44. Vogelius, Ivan. Postdoc, RH. WP09 leader.
45. Wojdacz, Tomasz. Postdoc, AU.
46. Østergaard, Leif. Professor, AUH. WP04 leader.